Effect of multi-intervention with a small dose of propofol and dexamethasone compared with dexamethasone alone on postoperative nausea and vomiting in pediatric moyamoya patients

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ABSTRACT

Effect of multi-intervention with a small dose of propofol and dexamethasone compared with dexamethasone alone on postoperative nausea and vomiting in pediatric moyamoya patients

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Background: Pediatric moyamoya patients undergoing encephalo-duro-arterio-synangiosis (EDAS) surgery are at high risk for postoperative nausea and vomiting (PONV). This prospective, randomized, observer-blind study was designed to evaluate the antiemetic effect of subhypnotic dose of propofol combined with dexamethasone.

Method: Sixty moyamoya patients who were aged 4-17 yr and underwent EDAS surgery under standardized anesthetic technique followed by postoperative pain control with fentanyl i.v. infusion were included. At dural closure, we administered either normal saline and 0.15 mg/kg dexamethasone (Group D) or 0.5 mg/kg propofol and 0.15 mg/kg dexamethasone (Group DP). As statistical analysis, generalized linear mixed model (GLMM) for repeated measure binary outcomes (nausea and vomiting) and also linear mixed model (LMM) for repeated measure continuous outcome (pain score) were used. Time and group were modeled as fixed effects with primary objectives as the dependent variables. P value of less than 0.05 was considered significant.

Result: The incidence of nausea and vomiting did not differ between two groups during study period. More than 80% of patients in Group D and 63.3% of patients in Group DP complained of nausea during the early period (~ 6 hr) without statistical significance. The incidence of nausea in both groups decreased to 30-40% during the late period (6-24 hr). There were no differences

in the number of patients who required rescue antiemetic between the two groups.

Conclusion: A small dose of propofol combined with dexamethasone may not increase antiemetic effect in pediatric moyamoya patients undergoing EDAS surgery compared with prophylactic dexamethasone alone.

Key words : dexamethasone; moyamoya disease; PONV; propofol

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I. INTRODUCTION

Moyamoya disease, common in children, is a rare progressive ischemic vascular disorder in the territory of anterior and middle cerebral arteries. Neovascularization procedures such as direct or indirect vascular bypass surgery are effectively practiced in most institutes, including ours, for those patients. Intraoperative and postoperative management strategies are strictly based on the hemodynamic stability and normocarbic status. Recently, it is reported that postoperative neurologic deterioration is often caused by cerebral hemodynamic changes such as shift of the watershed area or hyperemia in brain regions.[1] Postoperative pain, nausea and vomiting activate the sympathetic nervous system and increase intracranial pressure. Therefore, strict postoperative patient care for pain and postoperative nausea and vomiting (PONV) while along with neurologic evaluation should be provided to pediatric myoamoya patients who underwent surgical corrections.[2] Continuous intravenous infusion with fentanyl[3] is effective for postoperative pain control in moyamoya patient, but this also contributes to additional risk factor for PONV in children.[4,5]

Prophylactic dexamethasone or ondansetron is known to reduce the risk of PONV by 26%,[6] but the antiemetic effect of ondansetron is uncertain in pediatric neurosurgical patients.[7] A small dose of propofol administered at the

end of surgery has shown antiemetic effect with shorter PACU stay in some surgical circumstances in child and female adults.[8,9] There has been no reported incidence of PONV in pediatric moyamoya patients undergoing surgical correction, especially receiving fentanyl as postoperative pain control. It is recommended to treat high risk patients with multi-antiemetic interventions[10] because most antiemetic interventions work independently of each other and independently of the patient's risk factor.[6] Previous studies showed additional or synergic effect of a combination of propofol and dexamethasone on PONV in pediatric or adult patients.[11,12]

Therefore, we investigated whether a subhypnotic dose of propofol presents antiemetic effect in pediatric moyamoya patients on prophylactic dexamethasone undergoing indirect vascular bypass surgery and receiving with fentanyl infusion for postoperative pain control.

II. MATERIALS AND METHODS

In this prospective, randomized, and observer-blind study, we included 67 patients who were in ASA physical status I or II, diagnosed with moyamoya disease, aged 4-17 yr, and scheduled for EDAS surgery. This study was approved by the institutional review board, and informed consent was obtained from patients' parents. Exclusion criteria included mental retardation, presence of neurologic sign, seizure, history of motion sickness or previous PONV at admission and requirement of prolonged postoperative ventilator care.

Patients fasted for 4-8 hours before surgery according to age. No premedication was given to any patients. As patients arrived at the preinduction room with their parents, thiopental sodium 2 mg/kg was administered to children who were crying or anxious about entering the operating room. Anesthesia was induced with intravenous thiopental sodium 3-5 mg/kg followed by face mask ventilation with sevoflurane in air and oxygen. The trachea was intubated with the aid of rocuronium 0.7 mg/kg. Anesthesia was maintained

with sevoflurane (2-4 vol%) in 50% oxygen and remifentanil infusion (infusion rate of 0.1-0.4 μg/kg/min), and anesthetic depth was adjusted to changes in the hemodynamic variables within 20% of baseline values. Controlled ventilation was also adjusted to maintain end-tidal carbon dioxide partial pressure of 35-40 mmHg. Body temperature was maintained within 36.0-36.7°C with air heater. Patients were continuously monitored using standard anesthetic monitors of ECG, continual invasive blood pressure, and pulse oximetry. For postoperative pain control, fentanyl i.v. infusion at 0.5 μg/kg/hr (with the maximum dose of 600 μg/day) began at dural closure and continued for 48 hours postoperatively (infusion rate was adjusted to avoid over-sedation). At the completion of surgery, residual muscle relaxation was completely reversed with neostigmine 0.02 mg/kg and atropine 0.01 mg/kg after regaining spontaneous ventilation. After completion of the head dressing, anesthetics were discontinued and the trachea was extubated. Patients stayed in the postanesthetic care unit (PACU) for 1 hour, and were moved to a general ward.

Patients were randomly assigned with computer-generated random numbers and allocated into two groups; dexamethasone group (Group D) and dexamethasone and propofol group (Group DP). Experimental drugs were administered at dural closure; normal saline and dexamethasone 0.15 mg/kg in Group D and propofol 0.5 mg/kg and dexamethasone 0.15 mg/kg in Group DP. In the PACU and ward, nursing staff caring for the patients recorded every episode of nausea and vomiting for 24 hours (at the interval of 0-2 hr, 2-6 hr, 6-12 hr and 12-24 hr). Nausea, especially in younger children, was evaluated based on parents' observation. Otherwise children were asked about any occurrence of nausea and vomiting. Nausea and vomiting were defined as the expulsion of gastric contents or not, and retching was not discriminated from nausea because the subjects were children. When vomiting occurred more than twice in 30 minutes or patients were intolerant to vomiting, ondansetron 0.15 mg/kg was administered as rescue antiemetic. In addition, numeric scaled pain

scores (0-5, Wong-Baker's facial expression scale)[3] were evaluated. Ketorolac 1 mg/kg was intravenously administered upon request as rescue analgesic.

Collected data included gender, age, weight, height, duration of anesthesia and operation, occurrence of nausea and vomiting, pain severity, and number of patients who were administered with rescue antiemetic or analgesic. Awakening time (from discontinuation of anesthetics to regaining of orientation) was recorded. The nursing staff was aware of the nature of this study but unaware of patient group allocation.

Power analysis estimated the sample size of 30 in each group, which would detect 50% difference in the occurrence (80%) of nauseous patients with treatment during 24 hours postoperatively (power of 0.9 with α=0.05).

Student t-test or Mann-Whitney Rank Sum test, and chi-square test were used for comparison of mean data and dichotomous data, respectively. We tested the hypothesis using generalized linear mixed model (GLMM) for repeated measure binary outcomes (nausea and vomiting) and also linear mixed model (LMM) for repeated measure continuous outcome (pain score). Time and group were modeled as fixed effects with primary objectives as the dependent variables. P value of less than 0.05 was considered significant. Statistical analysis was performed with SAS 9.2 for Windows (SAS Institute Inc., Cary, NC, USA).

III. RESULTS

Among 67 patients, 60 pediatric moyamoya patients undergoing EDAS surgery were enrolled in this study (Group D=30, Group DP=30) (Figure 1).

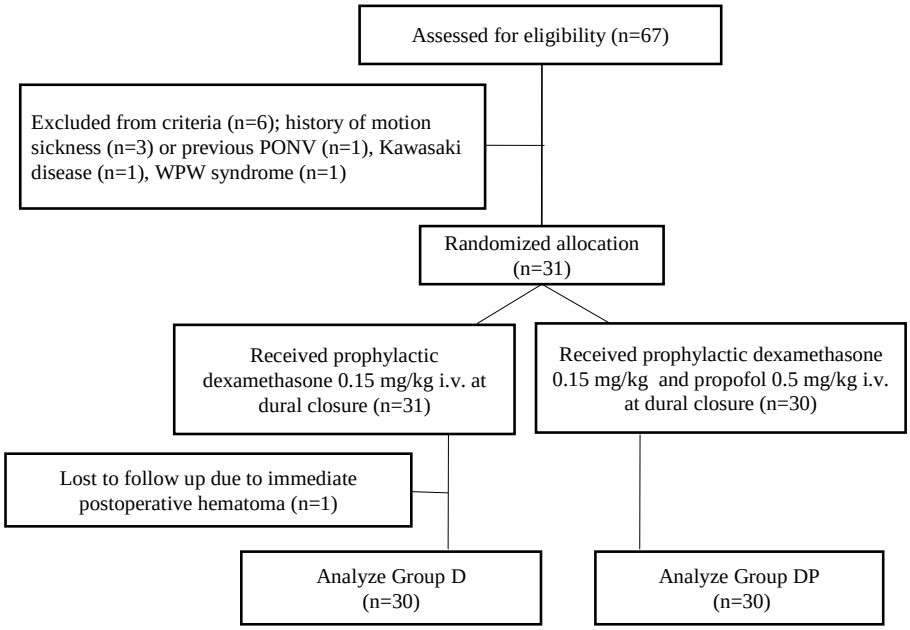

Figure 1. Flow chart to track participants through randomized trial.

Seven patients were excluded in the data collection step because of immediate postoperative hematoma (one patient), concomitantly carrying Kawasaki disease (one patient) and WPW syndrome (one patient), and history of motion sickness (three patients) or previous PONV (one patient).

In comparison of demographic data between the two groups, the mean age in Group DP was a little older than in Group D (10.0 yr vs. 8.1 yr, p=0.052), and accordingly patients of Group DP were significantly heavier than those of Group D (34.7 kg vs. 27.3kg, p=0.042). Otherwise, there were no differences between the two groups (Table 1).

In detail, fentanyl consumption dose during 24 hours based on body weight (10.7 mg/kg in Group D vs. 11.1 mg/kg in Group DP, p=0.534), awakening time (14.3 minutes in Group D vs. 12.1 minutes in Group DP, p=0.382) were not different between two groups.

Table 1. Demographic data

	Group D (n=30)	Group DP (n=30)	p-value
Sex (M/F)[a]	16/14	13/17	0.438
Age(yr)[b]	8.1 ± 3.4	10.0 ± 3.9	0.052
Wt (kg)[b]	27.3 ± 11.5	34.7 ± 15.9	0.042
Ht (cm)[b]	127.5 ± 21.4	133.7 ± 20.5	0.257
Op. duration (min)[b]	119.3 ± 19.3	113.0 ± 26.9	0.299
Anes. duration (min)[b]	161.3 ± 23.3	165.1 ± 26.5	0.554
Awakening time (min)[b]	14.3 ± 8.4	12.1 ± 10.5	0.382
Fentanyl consumption(μg/kg)[b]	10.7 ± 2.6	11.1 ± 2.0	0.534
Rescue analgesic needed (no. of patients)[c]	14 (46.7%)	8 (26.7%)	0.108
Rescue antiemetic needed (no. of patients)[c]	14 (46.7%)	13 (43.3%)	0.795

Statistical analyses were performed using Chi-square test [a], Student t-test [b], or Mann-Whitney Rank Sum test [c].

More than 80% of patients in Group D complained of nausea in the early period (~ 6 hr) where as 63.3% of patients in Group DP did so (but statistically not significant). The incidence of nausea in both groups decreased to 30-40% in the late period (6-24 hr) (Table 2). This was also evident from GLMM for repeated measures analysis ($p<0.001$), but neither fixed factor of group ($p=0.146$) nor interaction of postoperative period and group ($p=0.146$) did show significant difference from test for fixed effects (Table 3) and type III test of fixed effects (Table 4). The odd ratio for nausea of group D over group DP was 1.814 (95% CI, 0.811-4.057). By GLMM for vomiting with fixed effects of postoperative periods and group, there were no statistical differences of fixed factor of postoperative period and group and interaction of both factors (Table 3). But by the type III test of fixed effects, postoperative periods showed only weak probability of 0.0275, but neither group ($p=0.8079$) nor interaction of postoperative period and group ($P=0.2411$) showed difference (Table 4)). The odd ratio for vomiting of group D over group DP was 1.108 (95% CI, 0.484-2.537. There was no difference in the number of patients who required rescue antiemetic (Table 1).

During postoperative 24 hours, only one patient in Group D and four patients in Group DP were free from nausea, and almost half the patients of each group were free from vomiting. Statistical analysis with linear mixed model (LMM) revealed that pain scores at early postoperative periods (0~6 hr) were higher than those at late periods in both groups (P=0.001) but did not differ between groups at measured intervals (Figure 2).

Table 2. Incidence of postoperative nausea and vomiting according to postoperative period

Postoperative period	Nausea		Vomiting	
	Group D	Group DP	Group D	Group DP
0-2 hr	25 (83.3%)	19 (63.3%)	2 (6.7%)	4 (13.3%)
2-6 hr	24 (80.0%)	19 (63.3%)	5 (16.7%)	7 (23.3%)
6-12 hr	11 (36.7%)	11 (36.7%)	12 (40.0%)	8 (26.7%)
12-24 hr	12 (40.0%)	10 (33.3%)	9 (30.0%)	4 (13.3%)
Overall Complete response	1 (3.3%)	4(13.3%)	14 (46.7%)	14 (46.7%)

Data are no. of patients (%). Generalized linear mixed model (GLMM) for repeated measured was performed. Time (postoperative period) and group were modeled as fixed effects with primary objectives as the dependent variables (nausea and vomiting). P value of less than 0.05 was considered significant. There were no significant difference between two groups and of fixed effects of time x group. See the text.

Table 3. Statistical analysis of postoperative nausea and vomiting.

	Nausea			Vomiting		
		SE of	Pr>ltl		SE of	Pr>ltl
Intercept	-0.7731	0.4542	0.0941	-1.9319	0.5648	0.0012
Time (vs. 12-24 hr)						
0-2 hr	1.3897	0.5747	0.0166	0	0.7680	1
2-6 hr	1.3897	0.5747	0.0166	0.7009	0.6982	0.3168
6-12 hr	0.1639	0.5729	0.7751	0.8849	0.6867	0.1992
Group	0.3234	0.6319	0.6094	1.0433	0.7133	0.1454
Time x group						
0-2 hr	0.8240	0.8643	0.3417	-1.8490	1.1409	0.1069
2-6 hr	0.5857	0.8451	0.4892	-1.4952	0.9500	0.1173
6-12 hr	-0.3209	0.8016	0.6894	-0.4199	0.8859	0.6361

Generalized linear mixed models analysis was used. Time refers to postoperative period. β; estimate. Group consists of dexamethasone and propofol group (Group DP) and dexamethasone group (Group D), respectively.

Table 4. Type III test of fixed effects of postoperative nausea and vomiting.

Effect	Num DF	Den DF	F value	Pr>F
Nausea				
Time	3	174	10.93	<0.001
Group	1	174	2.13	0.1459
Time x Group	3	174	2.40	0.5261
Vomiting				
Time	3	174	3.12	0.0275
Group	1	174	0.06	0.8079
Time x Group	3	174	1.41	0.2411

Generalized linear mixed model (GLMM) was performed. Time refers to postoperative period. Group consists of dexamethasone and propofol group (Group DP, n=30) and dexamethasone group (Group D, n=30), respectively. Num DF; degree of freedom of the numerator, Den DF; degree of freedom of the denominator. Two-tailed significance probability at p value of 0.05 was considered as statistical significance.

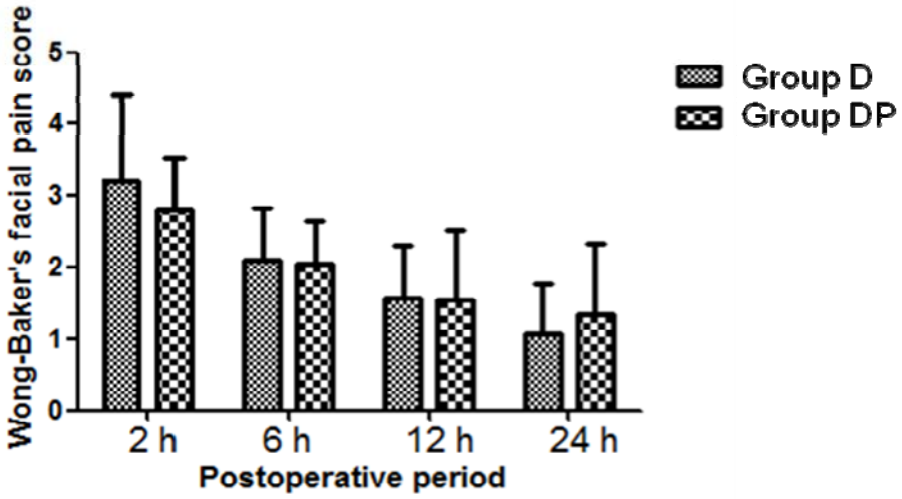

Figure 2. Postoperative Wong-Baker's facial pain score.

There are no differences in postoperative pain score between group D (dexamethaxone alone, n=30) and group DP (dexamethasone and propofol, n=30). Data are presented as the mean and SDM. Statistical analysis with linear mixed model (LMM) revealed that pain scores at early postoperative periods (0~6 hr) were higher than those at late periods in both groups (P=0.001) but did not differ between groups at measured intervals.

IV. DISCUSSION

This study suggests that propofol 0.5 mg/kg given at dural closure may not exert the additive or synergic effect to dexamethasone on PONV even though it slightly decreased the incidence of nausea by 20 % in early postoperative period (but statistically insignificant). Analysis by generalized linear mixed model for repeated measures revealed that the odd ratios for nausea and vomiting of group D over group DP were 1.108 (95% CI, 0.484-2.537) and 1.814 (95% CI, 0.811-4.057), respectively.

Even though our sample size of 60 patients is relatively small and has lower power, the aim of this study to test antiemetic effect of small dose of propofol was confined to the pediatric moyamoya patients undergoing surgical correction. To test our hypothesis that multi-interventions for PONV using small dose of

propofol combined with dexamethasone would exert better effects to PONV than dexamethasone alone, we performed generalized linear mixed model repeated measures which attain the correct sample size with lower power. [13]

Although the incidence of PONV in pediatric moyamoya patients has not been reported, the overall incidence of nausea and vomiting in our study is inconsistent to previous studies for craniectomy patients.[14,15] Roberts et al. reported the influence of postoperative opioid on PONV in a dose-dependent manner; the overall postoperative nausea (PON) and postoperative vomiting (POV) in elderly patients receiving postoperative opioid were 51.3% and 23.8%, respectively.[14] According to Wig et al.,[15] the incidence of nausea and vomiting in adult patients undergoing craniectomy with prophylactic dexamethasone was 54.3% and 45.7%, respectively. Perhaps these differences may be attributed to three main factors: children vs. adults, moyamoya disease vs. supratentorial tumor, and postoperative use of fentanyl or not.

We could not explain the reason why prophylactic use of propofol 0.5 mg/kg did not show the additive or synergistic effect on PONV over dexamethasone which might prevent the occurrence of vomiting even during the early period.[4] Perhaps our results may be explained in part by the dose-related antiemetic effect of propofol because propofol plasma concentration should reach 343 ng/ml to reduce POV by 50%.[16] Therefore, the incidence of nausea in propofol group might remain low only during the early postoperative period. Our findings are inconsistent with the fact that most antiemetic interventions work independently of each other,[6] if propofol shows antiemetic effect at lower plasma concentration than 343ng/ml. In adults undergoing laparoscopic surgery, propofol with a small dose followed by infusion did not show antiemetic effect.[17] Perhaps a prophylactic dose of propofol 0.5 mg/kg is too small to present synergistic effect with dexamethasone in high risk neurosurgical pediatric patients because enhanced antiemetic effects of propofol in combination with dexamethasone were shown in less risky patients.[11,18] Our

demographic data showed that the two groups were different only in body weight. Although patients of Group DP were heavier than those of Group D, fentanyl consumption dose based on body weight was the same between two groups. Therefore, we do not think difference in body weight affected our results because we controlled for most risk factors to compare two groups. Even though the effect of dexamethasone on PONV was not the primary end point in our study, prophylactic dexamethasone regardless of propofol completely prevented the occurrence of POV in 50% of patients.

Moyamoya disease is diagnosed with unique cerebral angiographic finding frequently accompanied with transient ischemic attacks or seizures. The nature of this disease is progressive, and neovascularization procedures such as direct or indirect vascular bypass surgery prevent further aggravation and improve the occurrence of neurologic symptoms. However, postoperative neurologic deterioration is related with dynamic changes in bypassed vasculatures.[1] Therefore, highly qualified postoperative pain control is needed to avoid abrupt fluctuations in blood pressure, anxiety, and hypo- or hyper-ventilatory status as well as not to mask any possible neurologic deterioration. As postoperative pain control, our institutional regimen includes prophylactic dexamethasone and continuous fentanyl infusion. Therefore our patients must be subject to PONV because the incidence of PONV increases with baseline risk factor, including children, volatile anesthetics and remifentanil used as anesthetic maintenance, and fentanyl infusion as postoperative pain control.[10] At present, the exact mechanisms of PON and POV in association with separate risk factors are not uncovered completely. Even though prophylactic ondansetron which was used to prevent PONV in neurosurgical cases resulted in different success rates according to age, gender or nature of surgical procedures,[7,15,19,20] strategies using multi-antiemetic interventions are needed for high risk pediatric neurosurgical patients. As postoperative pain scores decreased as time passed in both groups, adjustment of fentanyl infusion rate or addition of NSAIDs needs to be

considered.

V. CONCLUSION

A small dose of propofol combined with dexamethasone may not increase antiemetic effect in pediatric moyamoya patients undergoing EDAS surgery compared with prophylactic dexamethasone alone.

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< ABSTRACT (IN KOREAN)>

소아 모야모야 환자의 술 후 구역 구토에 대한 소량의 propofol-dexamethasone 병용 투여와 dexamethasone 단독 투여의 효과 비교

<지도교수 민 경 태>

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김 정 민

배경: Encephalo-duro-arterio-synangiosis (EDAS)수술을 받는 소아 모야모야 환자들은 술 후 오심 구토의 고 위험군에 속한다. 따라서 이 연구는 소아 모야모야 환자들을 대상으로 소량의 propofol을 dexamethasone과 병용 투여 시 propofol의 항 구토 효과를 보는 전향적, 무작위 관찰자 맹검 임상연구를 계획하였다.

방법: EDAS 수술을 받는 4-17세 60명의 환자를 대상으로 일반적인 전신 마취 방법을 적용하고, 술 후 통증 조절을 위해서 fentanyl을 지속 정주하였다. 경막을 닫을 때, D군에는 dexamethasone 0.15 mg/kg 과 식염수를 정주하고, DP군에는 dexamethasone 0.15 mg/kg 과 propofol 0.5 mg/kg을 정주하였다. 통계분석을 위해서 반복 측정된 구역, 구토의 이항 자료와, 역시 반복 측정된 연속 형 자료인 술 후 통증 지수 대해서는 일반화 선형 혼합 모형(generalized linear mixed model)을 이용하여 통계 분석하였다. 시간과 그룹을 종속변수로서 분석의 우선적 목표로 정하고, 고정효과로 설정하여 분석하였다. P값은 0.05 미만을 통계적으로 유의 하다고 고려하였다.

결과: 두 그룹 간 통증 사정 점수나 각성까지 걸린 시간의 차이는

없었다. D군의 80%이상과, DP군의 63.3%에서 술 후 조기 6시간 이내에 오심을 호소하였으나, 두 군간의 통계적 차이는 없었다. 두군 모두 술 후 24시간 이내 6시간 이후 오심의 발생 빈도는 30~40%로 감소하였다. 두 군간 추가 항 구토제 요구를 하는 환자의 발생 수나 구토의 발생 횟수간에는 차이가 없었다.

결론: EDAS 수술을 받는 소아 모야모야 환자에게서 propofol 0.5 mg/kg과 dexamethasone 병용 투여는 예방적 dexamethasone 단독 투여에 비해 술 후 항 구토효과의 차이가 나지 않았다.

핵심되는 말 : dexamethasone; 모야모야병; 술 후 구역 구토; propofol